REMARKS

Claims 6-18 and 26 were pending in the application. Claims 14 and 15 have been canceled without prejudice and claims 6, 7, 16, and 26 have been amended. Accordingly, upon entry of the amendments presented herein, claims 6-13, 16-18, and 26 will remain pending in the application.

Support for the amendments to the claims may be found throughout the specification and claims as originally filed. Specifically, support for the amendment to claim 6 may be found in, for example, originally presented claim 15 and at page 9, lines 3-7 of the specification. *No new matter has been added by the foregoing claim amendments.*

Any amendments to and/or cancellation of the claims are not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Withdrawal of Certain Objections/Rejections

Applicants gratefully acknowledge the Examiner's indication that the following objections/rejections have been withdrawn:

a) the previous rejection of claims 1-3, 9, and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the phrases "test compound" and "biological target";

b) the previous rejection of claims 1-18 and 26 under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the phrases "fractions thereof" and "portions thereof";

c) the previous rejection of claims 3 and 7 under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the phrase "saturating amount";

d) the previous rejection of claims 3 and 7 under 35 U.S.C. § 112, second paragraph, as being indefinite for use of the phrase "substantially all of the free biological target";

e) the previous rejection of claims 1-17 under 35 U.S.C. §103(a) as being unpatentable over Turk *et al.* ((1999) *Chem. Biol.* 6:823-833) in view of Soker *et al.* (US 2005/0112063); and

f) the previous rejection of claims 1-17 under 35 U.S.C. §103(a) as being obvious over Griffiths, *et al.* ((1998) *Proc. Natl. Acad. Sci., USA* 95:15183-15188) in view of Soker *et al.* (US 2005/0112063).

Claim Objections

The Examiner has objected to claim 26 because, according to the Examiner, "it contains two method steps labeled (c) whereas one should be labeled as step (e)."

Applicants respectfully submit that claim 26 does not contain a step (e). Rather, the second recitation of step (c) in claim 26, following step (d), is a reference back to the amount of free MetAP-2 that is determined in step (c). Specifically, step (d) of claim 26 requires that the amount of free MetAP-2 that is determined in step (c) be compared with the amount of MetAP-2 in a control sample. ***Following step (d), claim 26 further requires that a decrease in the amount of free MetAP-2 in each of the biological samples determined in step (c) compared to the amount in the control sample is a measure of the extent of inactivation of MetAP-2 in each of the biological samples.***

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection of claim 26.

Rejection of Claims 6-13 Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner has rejected claims 6-13 under 35 U.S.C. 112 § first paragraph, because, according to the Examiner,

> the specification, while ***being enabling for ovalicin, fumagillin, fumagillol, and fumagillin analogs*** does not reasonably provide enablement for all "test compounds that are inhibitors of MetAP-2". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to utilize the invention commensurate in scope with these claims. (Emphasis added).

Without acquiescing to the validity of the Examiner's rejection, and solely in the interest of expediting prosecution and allowance of the pending claims, Applicants have amended claim 6 to be directed to a test compound which is an inhibitor of MetAP-2, wherein ***the inhibitor of MetAP-2 is a fumagillin anologue***, thereby rendering the foregoing rejection moot.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 6-13.

Rejection of Claims 6-17 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 6-17 under 35 U.S.C. § 112, first paragraph, as allegedly "failing to comply with the written description requirement." In particular, the Examiner is of the opinion that

> Applicant has not described in a reasonable generic manner to show support for any test compound that may have the activity of being an inhibitor of MetAP-2. Applicant has not described a correlation of between the structure and function for the test compounds of the instant claims and also the assays for determining the test compound of the instant claims are not described. Thus, the assays for determining the compounds do not provide a description of the structural/physical or chemical features required for the test compounds of the instant claims.

Applicants traverse this rejection for at least the following reasons. An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicants were in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). In the present case, the claimed invention is <u>not</u> the MetAP-2 inhibitor compounds, but rather, <u>methods</u> for determining the extent of inactivation of MetAP-2 in a biological sample which includes the step of administering to a subject a test compound which is an inhibitor of MetAP-2, wherein the inhibitor is a fumagillin analogue.

Applicants' specification provides ample guidance to one of skill in the art regarding *the claimed methods* for determining the effect of a test compound which is an inhibitor of MetAP-2, wherein the MetAP-2 inhibitor is a fumagillin analogue, on the extent of inactivation of

MetAP-2 in a biological sample. For example, Applicants' specification teaches that a test compound may be administered to a subject "via any suitable route, such as parenteral, including intramuscular, intravenous, subcutaneous and intraperitoneal injection; or the buccal, oral, vaginal, rectal, ocular, intraocular, intranasal, topical, intradermal or transdermal route." Applicants' specification further teaches that a test compound may be "formulated for administration using methods known in the art and preferably in a manner which is consistent with the chemical properties of the test compound and the intended route of administration." In addition, Applicants' specification teaches that a plurality of biological samples, such as "whole blood, a blood fraction or a particular collection of blood cells, such as erythrocytes, white blood cells, T-cells, B-cells, macrophages, or other professional antigen-presenting cells; leukemic cells, lymphoma cells, tumor tissue; cancer cells; bone marrow; synovium, synovial fluid, cerebrospinal fluid, skin, liver tissue or cells, heart tissue, lung tissue, brain tissue, muscle tissue, bone, epithelium, endothelium, prostate tissue, breast tissue, lymph nodes, and spleen" may be removed and, optionally, processed using methods known in the art, such as, isolation of a particular cell type from within the biological sample, tissue homogenization, and cell lysis (see, *e.g.,* page 10, lines 12-35 of the specification).

With respect to suitable methods of determining the amount of free MetAP-2 within each of the plurality of biological samples, Applicants' specification teaches that the amount of free MetAP-2 may be determined by measuring the MetAP-2 enzyme activity in the sample and by determining the amount of MetAP-2-inhibitor complexed with a quantifiable MetAP-2 inhibitor (see, *e.g.,* page 6, line 17, through page 7, line 27 and page 8, line 32, through page 9, line 2 of the specification and references disclosed therein). Applicants' specification also provides suitable quantifiable MetAP-2 inhibitors (see, *e.g.,* page 11, line 35, through page 14, line 20 of the specification) and suitable controls and methods to determine the amount of free MetAP-2 in such control samples for use in the claimed methods (see, *e.g.*, page 7, line 28, through page 8, line 28 of the specification).

Applicants' specification also contains an extensive disclosure relevant to MetAP-2 inhibitors which can be tested using the claimed methods. For example, at page 8, line 33, though page 9, line 2 and lines 24-27 of the specification, Applicants disclose that suitable MetAP-2 inhibitors include ovalicin, fumagillin, fumagillol and fumagillin analogues, and incorporate by reference numerous U.S. Patents and PCT publication teaching a plethora of fumagillin analogues suitable for use in the claimed methods. Applicants also respectfully point

out to the Examiner that the references upon which the Examiner relies, Turk, *et al.* and Griffiths, *et al.* also teach numerous fumagillin analogues that were known in the art at the time of the invention.

Thus, based on the extensive teachings in Applicants' specification regarding methods for determining the extent of inactivation of a test compound that is an inhibitor of MetAP-2, wherein the compound is a fumagillin analogue, suitable fumagillin analogues, as well as the knowledge generally available in the art, the skilled artisan would understand that Applicants were in possession of the claimed invention at the time of filing. Accordingly, the requirement of 35 U.S.C. § 112, First Paragraph for written description has been satisfied and Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to claims 6-17.

Rejection of Claims 6-13 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 6-13 under 35 U.S.C. §112, second paragraph as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> [i]t is unclear as to which test compound or biological target to use for the method of measuring the ability of a test compound to inactivate a biological target in the instant claims 6-13. The administration of different compound will vary with regards to dose or the biological target of interest. The recitation of a "test compound which is an inhibitor of a biological target" does not impart any physical or structural characteristics necessary for the test compounds of the instant claims to indicate the scope of the claimed compounds.

Applicants respectfully traverse the foregoing rejection on the grounds that, based on the plain language of the claims, the teachings in the specification, and the general knowledge in the art, one of skill in the art would find the phrase "a test compound which is an inhibitor of MetAP-2" to be clear and definite.

For example, Applicants' specification teaches at page 9, lines 13-18 that a suitable inhibitor

> interacts with the active site of the MetAP-2 enzyme, such that, once a molecule of the test compound contacts a molecule of MetAP-2, it resides in the active site of the enzyme and blocks the reaction of the MetAP-2 molecule with another inhibitor molecule. The test compound can also be a compound which inhibits MetAP-2 by binding to a site on MetAP-2 other than the active site.

At page 9, lines 18-22, Applicants' specification further teaches that a MetAP-2 inhibitor that is an irreversible inhibitor of MetAP-2

> inhibits MetAP-2 enzymatic activity and dissociates from the enzyme sufficiently slowly such that on the time scale of the method of the invention, very little of it would be expected to dissociate from the enzyme.

In addition, Applicants' specification teaches that an irreversible inhibitor of, for example, MetAP-2,

> is a compound which inhibits the biological target and has a rate of dissociation from the biological target which is slow relative to the length of time required to complete the assay. For example, if the test compound dissociates from the biological target at a rate k, then 50% of the originally inactivated biological target will remain inactivated at about time $0.69302/k$. It is thus preferred that the assay be completed in a time period, t, of less than about $0.7/k$, $0.6/k$, $0.5/k$, $0.4/k$, $0.3/k$, $0.2/k$ or $0.1/k$. In one embodiment, the irreversible inhibitor reacts with the biological target to form a covalent bond. (See, *e.g.*, page 9, lines 3-12 of the specification).

Furthermore, as evidenced by the references cited by the Examiner (*i.e.*, Turk, *et al.* and Griffiths, *et al.*), as well as the references incorporated in Applicants' specification (see, for example, page 8, line 34, through page 9, line 2, and page 9, lines 26-27 of the specification) the terms "inhibitors of MetAP-2" and "MetAP-2 inhibitors" were well known in the art at the time of the invention.

In view of the foregoing, it is evident that claim 6, and claims dependent therefrom, are clear and definite. Accordingly, Applicants respectfully request that this rejection of claims 6-13 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejection of Claims 6-17 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 6-17 under 35 U.S.C. §103(a) as being unpatentable over Turk *et al.* ((1999) *Chem. Biol.* 6:823-833) in view of Soker *et al.* (US 2005/0112063). In particular, the Examiner has asserted that Turk, *et al.* teach the treatment of bovine aortic endothelial cells with the fumagillin analog TNP-470 and the subsequent lysing of the cells for determining the level of inhibition of MetAP2 (see, Office Action dated May 18, 2007). Although the Examiner concedes that "Turk *et al.* does not teach of [sic] the administration of the fumagillin analog to a subject or removing biological samples from the subject", the Examiner asserts that

> Soker *et al.* teaches of [sic] the method of measuring the ability of a test compound to inhibit a biological target *via* the administration of an antiangiogenic compound, such as a polymer conjugated TNP-470 to a subject *in vitro* or *in vivo* and assessing the bioeffectiveness of the compound *via* the removal of a sample (*i.e.* blood) from the subject. Also, Soker *et al.* teaches that the excision of the liver shows inhibition of liver regeneration upon treatment with TNP-470 which is an antiangiogenic compound. It would be obvious to one skilled in the art that a sample or multiple samples (*i.e.* blood) taken from a patient can be used to measure the ability of the test compound to inhibit a biological target. Also, it would be obvious that the measure of the inhibition of regeneration of a liver sample taken from a subject is a direct correlation of the inhibition of angiogenesis as TNP-470 is an antiangiogenic compound. Therefore a plurality of samples (*i.e.* blood, liver) can be removed from the subject to measure the ability of a test compound to inhibit a biological target.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references would have rendered the claimed invention obvious to the ordinarily skilled artisan at the time of the invention for the following reasons. Claim 6, and claims dependent therefrom, are directed to methods for determining the extent of inactivation of MetAP-2 in a biological sample derived from a subject, comprising the steps of (a) administering a test compound which is an inhibitor of MetAP-2 to the subject, wherein the inhibitor of MetAP-2 is a fumagillin anologue, wherein any MetAP-2 in the body of the subject that reacts with the test compound is inactivated MetAP-2 and any MetAP-2 that does not react with the test compound is free MetAP-2, (b) *removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject, and (c) determining the amount of free MetAP-2 within each of plurality of the*

biological samples, and (d) comparing the amounts determined in step (c) with the amount determined in a control sample, wherein a decrease in the amounts in each of the samples determined in step (c) compared to the amount in the control sample is a measure of the extent of inactivation of MetAP-2 in each of the biological samples.

The test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Takeda Chem. Indus., Ltd. v. Alpharma Pty.*, Ltd., 2007 U.S. App. LEXIS 15349, at *13 (Fed. Cir. 2007). "While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination. *Id.* at *13-14 (quoting KSR, 127 S. Ct. at 1731). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR*, 127 S. Ct. at 1731. ***Furthermore, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. § 2143).***

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references, alone or in combination, fail to teach or suggest each element of the claimed methods. As acknowledged by the Examiner, Turk *et al.* fail to teach or suggest ***administering a test compound to a subject.*** The Examiner has also conceded that there is no teaching or suggestion in Turk *et al.* that a single biological sample may be removed from the subject, let alone ***that a plurality of biological samples may be removed from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject,*** as required by the pending claims. Thus, Turk *et al.* fail to teach or suggest the claimed methods.

The secondary reference relied on by the Examiner, Soker *et al.*, does not make up for the deficiencies in the primary reference. Specifically, Soker *et al.* teach that the bioeffectiveness of TNP-40, an anti-angiogenic compound, may be assessed by determining ***the amount of a protein in a single bodily fluid*** derived from a subject (see, *e.g.,* page 2, [0020] of Soker *et al.*). Soker *et al.* teach that the determination of the amount of a protein in the biological sample before and after treatment with the anti-angiogenic compound is an indicator of the effect of the compound on vascular permeability which manifests in the subject as elevated protein levels, *i.e.,* proteinuria

(see, *e.g.*, page 1, [0006] and page 7, [0073] of Soker *et al.*). However, there is ***no teaching or suggestion in Soker, et al. that the amount of free MetAP-2 is, or can be, determined in such a single bodily fluid***.

Furthermore, although Soker *et al.* teach that the bioeffectiveness of an anti-angiogenic compound on endothelial cell proliferation may be assessed by observing liver regeneration in mice receiving a 2/3 hepatectomy (see, e.g., page 9, [0100] and page 10, [[0106]), ***Soker et al. fail to teach or suggest that the excised liver is, or may be, used to determine the amount of free MetAP-2*** in the ***single biological sample***.

Moreover, in contrast to the Examiner's assertions that based on the teachings of Soker *et al.* it "would be obvious to the skilled artisan that the measure of the inhibition of regeneration of a liver sample taken from a subject is a direct correlation of the inhibition of angiogenesis as TNP-470 is an antiangiogenic compound", Applicants submit that ***there is no teaching or suggestion in Soker et al. that inhibition of cell proliferation by the anti-angiogenic compound in a biological sample is correlated with the amount of free MetAP-2 in the biological sample***.

Therefore, since Soker *et al.* merely teach that protein levels can be measured in a single bodily fluid to determine if proteinuria is present, and cell proliferation can be assessed in a single biological sample, such as liver, Applicants submit that ***Soker et al. fail to teach or suggest removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject, and determining the amount of free MetAP-2 within each of plurality of the biological samples***. Thus, Soker *et al.* also fail to teach or suggest the claimed methods.

In view of the foregoing, it is evident that, Turk *et al.* and/or Soker *et al.*, either alone or in combination, fail to teach or suggest each element of the claimed invention and, thus, fail to render the claimed invention obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner has also rejected claims 6-17 under 35 U.S.C. §103(a) as allegedly being obvious over Griffiths, *et al.* ((1998) *Proc. Natl. Acad. Sci., USA* 95:15183-15188) in view of Soker *et al.* (US 2005/0112063). In particular, the Examiner has asserted that Griffiths, *et al.* discloses the incubation of recombinant human MetAP2 with ovalicin followed by incubation with fluorescein-fumagillin analog and the determination of the binding of the fluorescein-fumagillin analog to the MetAP2 (see, Office Action dated May 18, 2007). Although the

Examiner concedes that "Griffiths, *et al.* does not teach of [sic] the administration of the fumagillin analog to a subject or removing biological samples from the subject", the Examiner asserts that

> Soker *et al.* teaches of [sic] the method of measuring the ability of a test compound to inhibit a biological target *via* the administration of an antiangiogenic compound, such as a polymer conjugated TNP-470 to a subject *in vitro* or *in vivo* and assessing the bioeffectiveness of the compound via the removal of a sample (*i.e.* blood) from the subject. Also, Soker *et al.* teaches that the excision of the liver shows inhibition of liver regeneration upon treatment with TNP-470 which is an antiangiogenic compound. It would be obvious to one skilled in the art that a sample or multiple samples (*i.e.* blood) taken from a patient can be used to measure the ability of the test compound to inhibit a biological target. Also, it would be obvious that the measure of the inhibition of regeneration of a liver sample taken from a subject is a direct correlation of the inhibition of angiogenesis as TNP-470 is an antiangiogenic compound. Therefore a plurality of samples (*i.e.* blood/ liver) can be removed from the subject to measure the ability of a test compound to inhibit a biological target.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references would have rendered the claimed invention obvious to the ordinarily skilled artisan at the time of the invention for the following reasons. Claim 6, and claims dependent therefrom, are directed to methods for determining the extent of inactivation of MetAP-2 in a biological sample derived from a subject, comprising the steps of (a) administering a test compound which is an inhibitor of MetAP-2 to the subject, wherein the inhibitor of MetAP-2 is a fumagillin anologue, wherein any MetAP-2 in the body of the subject that reacts with the test compound is inactivated MetAP-2 and any MetAP-2 that does not react with the test compound is free MetAP-2, (b) ***removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject, and (c) determining the amount of free MetAP-2 within each of plurality of the biological samples,*** and (d) comparing the amounts determined in step (c) with the amount determined in a control sample, wherein a decrease in the amounts in each of the samples determined in step (c) compared to the amount in the control sample is a measure of the extent of inactivation of MetAP-2 in each of the biological samples.

As discussed above, the test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Takeda Chem.*

Indus., Ltd. v. Alpharma Pty., Ltd., 2007 U.S. App. LEXIS 15349, at *13 (Fed. Cir. 2007). "While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination. *Id.* at *13-14 (quoting KSR, 127 S. Ct. at 1731). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR*, 127 S. Ct. at 1731. ***Furthermore, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. § 2143).***

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references, alone or in combination, fail to teach or suggest each element of the claimed methods. As acknowledged by the Examiner, Griffiths *et al.* fail to teach or suggest ***administering a test compound to a subject*** or removing a single biological sample from the subject, let alone ***removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject***, as required by the pending claims. Thus, Griffiths *et al.* fail to teach or suggest the claimed methods.

The teachings of Soker *et al.* fail to make up for the deficiencies of Griffiths *et al.* in that Soker *et al.* fail to teach or suggest ***removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject, and determining the amount of free MetAP-2 within each of plurality of the biological samples***. Rather, as discussed above, Soker *et al.* teach methods for decreasing vascular hyperpermeability by administering an anti-angiogenic compound to a subject treated with a permeability inducing agent. Soker *et al.* teach that bioeffectiveness of an anti-angiogenic compound may be assessed by determining ***the amount of a protein in a single bodily fluid*** derived from a subject (see, *e.g.*, page 2, [0020] of Soker *et al.*). Soker *et al.* teach that the determination of the amount of a protein in the biological sample before and after treatment with the anti-angiogenic compound is an indicator of the effect of the compound on vascular permeability which manifests in the subject as elevated protein levels, *i.e.*, proteinuria (see, *e.g.*, page 1, [0006] and page 7, [0073] of Soker *et al.*). However, there is ***no teaching or suggestion in Soker, et al. that the amount of free MetAP-2 is, or can be, determined in such a single bodily fluid***.

Soker *et al.* also teach that the bioeffectiveness of an anti-angiogenic compound on endothelial cell proliferation may be assessed by observing liver regeneration in mice receiving a 2/3 hepatectomy (see, e.g., page 9, [0100] and page 10, [[0106]). However, ***Soker et al. fail to teach or suggest that the excised liver is, or may be, used to determine the amount of free anti-angiogenic compound*** in the ***single biological sample*** or that ***a plurality of biological samples are removed from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject.*** Furthermore, Soker *et al.* fail to teach or suggest that ***the amount of free MetAP-2 within each of the plurality of the biological samples is, or may be, determined.***

Applicants also submit that ***there is no teaching or suggestion in Soker et al. that inhibition of cell proliferation by the anti-angiogenic compound in a biological sample is correlated with the amount of free MetAP-2 in the biological sample.*** Thus, Soker *et al.* also fail to teach or suggest the claimed methods.

Therefore, since Soker *et al.* merely teach that protein levels can be measured in a single bodily fluid to determine if proteinuria is present, and cell proliferation can be assessed in a single biological sample, such as liver, Applicants submit that ***Soker et al. fail to teach or suggest removing a plurality of biological samples from the subject, wherein each of the plurality of biological samples is derived from a different tissue of the subject, and determining the amount of free MetAP-2 within each of plurality of the biological samples.*** Thus, Soker *et al.* also fail to teach or suggest the claimed methods.

In view of the foregoing, it is evident that, Griffiths *et al.* and/or Soker *et al.*, either alone or in combination, fail to teach or suggest the claimed invention and, thus, fail to render the claimed invention obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

SUMMARY

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. 12-0080, under Order No. PPI-144 from which the undersigned is authorized to draw.

Dated: **June 23, 2008**

Respectfully submitted,

By _____

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